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DN

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. |
|---|---|---|---|
| 08/954,954 | 10/21/97 | SUMMERS | N 2991/1 |

HM12/0429

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| EXAMINER | |
|---|---|
| KEMMERER,E | |
| **ART UNIT** | **PAPER NUMBER** |
| 1646 | 9 |

**DATE MAILED:** 04/29/99

**Please find below and/or attached an Office communication concerning this application or pr ceeding.**

**Commissioner of Patents and Trademarks**

| Office Action Summary | Application No. 08/954,954 | Applicant(s) Summers et al. |
|---|---|---|
| | Examiner Elizabeth C. Kemmerer | Group Art Unit 1646 |

☒ Responsive to communication(s) filed on *16 Feb 1999*.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

**Disposition of Claims**

☒ Claim(s) *1-22* is/are pending in the application.

Of the above, claim(s) *15-22* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-14* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☒ Claims *1-22* are subject to restriction or election requirement.

**Application Papers**

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. § 119**

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

**Attachment(s)**

☑ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *6*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

*--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---*

## DETAILED ACTION

### *Status of Application, Amendments, And/Or Claims*

The amendment filed 16 February 1999 (Paper No. 7) has been entered in full. Claims 15-22 remain withdraw from consideration as being directed to a non-elected invention. Claims 1-14 are pending and under examination.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

### *Withdrawn Objections And/Or Rejections*

The application is now fully in compliance with the sequence rules, 37 CFR 1.821-1.825.

The rejection of claims 1-14 under 35 U.S.C. § 112, second paragraph, as set forth at pp. 3-4 of the previous Office Action (Paper No. 5, 13 October 1998) is *withdrawn* in view of the amended claims. However, please see new rejection under 35 U.S.C. § 112, second paragraph, below.

### *New Matter*

Claims 11, 2, 5, 6 and 10-14 rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The specification does not disclose circular permuteins of EPO that have opening sites at the recited positions in **SEQ ID NO: 1**. Applicant may wish to review amended

claim 1, wherein it appears that "SEQ ID NO: 1" recited at line 17 of the claim may be a typographical error wherein "SEQ ID NO: 121" may have been intended.

***35 U.S.C. § 112, Second Paragraph***

Claims 1, 4, 9 and 11-14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 1 recites an improper Markush group. The word "and" should appear before "131-132" at line 27 of the claim. In claim 4, it is impossible for the polypeptide sequence GlyGlyGlySer (SEQ ID NO: 123) to also be a polypeptide sequence selected from the group consisting of SEQ ID NOS: 124-130. Amending claim 4 to recite "wherein the linker is selected from the group consisting of SEQ ID NO: 124, SEQ ID NO: 125, ... and SEQ ID NO: 130" is one way of resolving this issue.

***35 U.S.C. § 103***

Claims 1, 5 and 10-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pastan et al. in view of Lin as set forth at pp. 5-6 of the previous Office Action (Paper No. 5, 13 October 1998).

Applicant's arguments (pp. 11-16, Paper No. 7, 16 February 1999) have been fully considered but are not deemed to be persuasive for the following reasons.

Applicant urges that the prior art fails to provide a reasonable expectation of success, since the prior art shows that there is a high degree of unpredictability in the art. Applicant argues that '599 (also referred to as Pastan et al.) is limited to teaching only 2 circular permutation breakpoints of IL-4 in the context of a chimeric molecule, and that no circular permutations of IL-2, G-CSF or GM-CSF are shown to have activity. Applicant also asserts that the circularly permuted ligands are only useful when in the context of a chimeric molecule. Applicant also argues that '599 does not teach erythropoietin (EPO). This is not found to be persuasive, because Applicant's interpretation of Pastan et al. is too narrow. The patented claims themselves are evidence of this, since they embrace circular permutations of IL-4, IL-2, G-CSF and GM-CSF wherein the circular permutation breakpoint is at any place in the ligands. Once Pastan et al. disclosed that an active circular permutation could be made and screened for activity, it would have been a matter of routine experimentation to screen other circular permutations for activity. Pastan et al. also provide guidance regarding which breakpoints would be more likely to yield active circular permutations, and thus identifying which circular permutation variants would retain activity is not as unpredictable as Applicant asserts. Indeed, the instant claims embrace circular permutations of EPO with a breakpoint at any of 67 places, not all of which have been exemplified in the specification. However, no rejection has been made under 35 U.S.C. § 112, first paragraph, for lack of enabling disclosure commensurate in scope with the claims, because it would have been a matter of routine experimentation to determine which of the circular permutations would have the required activity, and because it sis legally permissible for the claims to embrace a reasonable number of inoperable embodiments. Regarding Applicant's

assertion that Pastan et al.'s disclosure only teaches that the circular permutation ligands are useful only in the context of a chimeric molecule, it is clear that the circular permutation ligand portion of the chimeric molecule is required to retain activity, and has this activity independent from the context of the chimeric molecule. See paragraph bridging columns 1-2. Finally contrary to Applicant's assertions, Pastan et al. do suggest that EPO would be amenable to this circular permutation procedure (column 4, line 40).

Applicant reviews several published prior art references as supporting their assertion that the results of circular permutation have been highly variable. Applicant concludes that, due to the complex nature of the structure/function relationship, one skilled in the art would not have a reasonable expectation of success of predicting which of the presently claimed molecules would have the desired activity. Applicant also states that Pastan et al. recognize this at the paragraph between columns 1 and 2. Again, this is not found to be persuasive, because Pastan et al.'s pioneering disclosure that active circular permutation variants of ligands could be made, and their guidance regarding what breakpoints should be selected with a greater chance of retaining activity, have reduced significantly the degree of unpredictability in the system. In the instant case, the secondary reference (Lin) discloses where in the EPO protein substitutions are tolerated. Taken in light of Pastan et al.'s disclosure that such places are likely to be good breakpoints, there is a reasonable expectation of successfully achieving the claimed invention.

Applicant urges that the generic speculation in '599 about general considerations for selecting breakpoints are not supported by the '599 specification. Applicant characterizes the general

guidelines as an invitation to experiment, and that it cannot be concluded that circular permutation is universally applicable to any protein. Applicant argues that the only exemplified breakpoints were glycosylation sites, and that substitution-tolerant sites were not exemplified. Applicant summarizes the teachings of '599 regarding breakpoints as unsubstantiated speculation. This is not found to be persuasive, because once Pastan et al. disclosed that circular permutation of ligands could yield active variants, it would have been routine to screen any particular circular permutation for activity. Also, it makes sound scientific sense that a breakpoint is more likely to be tolerated at a substitution-tolerant site, because a substitution-tolerant site is not essential for activity of the protein as a whole. Importantly, no evidence has been submitted to support Applicant's position that substitution-tolerant sites are not good breakpoints. Regarding Applicant's statement that it cannot be concluded that circular permutation can be applied to any protein, the Examiner is in agreement. A skilled artisan would not expect that a membrane-anchored protein such as a receptor kinase would be amenable to circular permutation. However, the skilled artisan would expect that other small soluble proteins such as cytokines, lymphokines and hormones would be amenable to circular permutation. This is what is suggested by Pastan et al. at column 4, wherein they specifically point to EPO as being amenable to the procedure. Therefore, Pastan et al.'s guidelines regarding suitable breakpoints are more than merely an invitation to experiment. Also, it is important to remember that the claimed invention is directed to circular permuteins of EPO with any one of 67 breakpoints, not all of which have been exemplified in the specification. No evidence of unexpected results for any *particular*

circular permutein of EPO has been submitted, nor is any *particular* circular permutein of EPO claimed.

Applicant argues that the disclosure of the secondary reference (Lin, or '008) does not teach individual sites at which amino acid substitutions can be made. Applicant characterizes Lin as disclosing an alignment of human and monkey EPO. Applicant asserts that substituting only one of these sites according to the alignment could not be expected to result in an active variant, but that all of the sites would have to be substituted to achieve an active variant. Applicant also urges that Lin's disclosure of substitutions at positions 95, 99, 105, 139 and 163 teach away from the claimed invention, since these are not identified in the instant specification as being appropriate breakpoints. Applicant also argues that the two sequences do not constitute a "family" of molecules from which it can be concluded which positions are conserved. This is not found to be persuasive, because it is not sound scientific reasoning that all of the positions must be substituted for retained activity. Artificially generated muteins having fewer substitutions are common. Lin discloses at column 11 that synthetic sequences that are partially duplicative of any of the two naturally occurring sequences could be made which retain activity. The disclosure of the alignment provides the skilled artisan with guidance as to which residues are not absolutely conserved. These would be good candidates for substitution. Regarding the disclosure of Lin regarding other substitution-tolerant sites which are not taught as appropriate breakpoints in the instant disclosure, it is not required that Pastan et al. in view of Lin point to only those points that would absolutely result in active circular permuteins. All that is required is a reasonable expectation of success. Lin points to several substitution-tolerant residues.

Pastan et al. teach that such are good *candidates* for breakpoint introduction. It would have been routine to screen for those breakpoints that resulted in active circular permuteins. It is important to remember that the claimed invention lists any of 67 potential breakpoints, not all of which have been exemplified in the specification. Surely, the claims embrace inoperative embodiments. However, this is legally permissible, since there would only be a reasonable number of inoperative embodiments, and the screening assay is disclosed such that the active permuteins could be easily identified by the skilled artisan. Regarding Applicant's comment that the two sequences of Lin do not constitute a family of molecules, the two molecules provide enough information to choose several potential breakpoints that are tolerant to substitution, which is all that is required.

Claims 1-4 and 6-9 rejected under 35 U.S.C. 103(a) as being unpatentable over Pastan et al. in view of Lin as applied to claims 1, 5 and 10-14 above, and further in view of Chaudhary et al. (1989, Nature 339:394-397) and Cousens et al. (U.S. Patent 4,751,180).

Pastan et al. in view of Lin teach circular permuteins of EPO embraced by claim 1, for example. Neither reference teaches GlySer-rich linker sequences as required by claims 2-4 and 6-9.

Chaudhary et al. disclose the use of a GlySer-rich linker for connecting antibody variable domains (see Figure 1a). Cousens et al., disclose that non-polar amino acids such as Gly and Ser are useful for a flexible linker (column 4).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to make the circular permuteins of EPO as taught by Pastan et al. in view of Lin,

and to modify that combined teaching by using GlySer-rich flexible linkers between the two portions of the circular permuteins as taught by Chaudhary et al. and Cousens et al. with a reasonable expectation at successfully achieving a circular permutein with sufficient flexibility in the linker for the two portions of the circular permutein to fold favorably for retained function. The motivation to do so is provided by the disclosures of Chaudhary et al. and Cousens et al. which disclose that the flexible linkers do not destroy activity.

Thus, the claimed invention as a whole was very clearly *prima facie* obvious over the prior art.

***Conclusion***

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elizabeth C. Kemmerer, Ph.D., whose telephone number is (703) 308-2673. The examiner can normally be reached on Mondays through Thursdays from 6:30 a.m. to 4:00 p.m. The examiner can also normally be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lila Feisee, can be reached on (703) 308-2731.

Official papers filed by fax should be directed to (703) 308-4242. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Elizabeth C. Kemmerer

ECK
April 23, 1999

ELIZABETH KEMMERER
PRIMARY EXAMINER